REMARKS

Claims 1-4, 6, 7, 9-11, 13, 25-28, 30, 31, 33-35, 37, 55, 58 and 59 are pending in the case.

In the Office Action, claims 1-4, 6, 7, 8-11, 13, 25-28, 30, 31, 33-35, 37, 55, 58 and 59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 1-4 and 58-59 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Wheelhouse *et al.* (U.S. Patent No. 6,087,493; hereafter "*Wheelhouse*").

Claims 1, 13, 25 and 58 are herein amended. No new matter has been introduced by the amendments.

Reconsideration of the present application in view of the foregoing amendments and the remarks below is respectfully requested.

Claim Rejections under 35 U.S.C. § 112

Claims 1-4, 6, 7, 8-11, 13, 25-28, 30, 31, 33-35, 37, 55, 58 and 59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Office Action states that the ranges for "m" and "p", respectively, conflict with the R moiety limitations regarding positive charge states.

Claims 1, 25 and 58 are herein amended with regard to the ranges of "m" and "p" so that they do not contradict to the R moiety limitations.

Further, the Office Action states that the parameter "n", defined as "equal to the absolute value of m/p", is vague and indefinite when "p = 0".

Claims 1, 25 and 58 are herein amended with regard to the definition of "n" for clarification purposes. The fact that dividing a number with zero is mathematically undefined is well known and the amendment does not introduce any new matter.

Regarding claims 58 and 59, the Office Action states that "Xp" in claim 58 lacks antecedent basis.

Claim 58 is herein amended to replace "Xp" with "X^{p}", which has proper antecedent basis.

Accordingly, the rejection of claims 1, 25 and 58 and their respective, direct or indirect dependent claims under 35 U.S.C. § 112, second paragraph, as being indefinite, should be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 1-4 and 58-59 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over *Wheelhouse*.

Specifically, the Office Action consistently maintain that the compounds recited in the present claims are disclosed in *Wheelhouse* and the latter also teaches inhibition of telomerase activity via G-quadruplex structure, via stabilizing or disrupting formation of such G-quadruplexes, which are polynucleotides. Therefore, it goes on to state, one of ordinary skill in the art would have been motivated to use the teaching of the *Wheelhouse* and induce apoptosis to cancer cells as claimed.

Applicant respectfully traverses the rejection.

Wheelhouse discloses porphyrin compounds that are effective telomerase inhibitors. Among the various porphyrin compounds disclosed, *Wheelhouse* established that those containing cationic porphyrin that can interact with quadruplex DNA by intercalation and can discriminate between duplex and quadruplex DNA, are the most

effective telomerase inhibitors (*see*, for example, ABSTRACT). Indeed, *Wheelhouse* emphasizes that the ability to interact with telomere DNA, *i.e.*, G-quadruplex DNA, rather than the ability to interact with telomerase per se, is the essential criteria for anti-cancer agents (*see*, for example, col. 15, lines 11-30; col. 16, lines 10-18 and lines 38-64). In particular, *Wheelhouse* focuses on meso-substituted porphyrins with substituted pyridines and quinolines, such as 5,10,15,20-tetra-(N-methyl-4-pyridyl)porphyrins (TMPyP4), which have appropriate sizes and positively-charged meso-substituents to stack nicely with the G-tetrads of quadruplex DNA and disrupts the helical structure of the adjacent DNA by intercalation (*see*, for example, col. 17, line 19 through col. 18, line 2; col. 20, line 8 through col. 24, line 66; and col. 44, lines 24-31).

In this connection, *Wheelhouse* tested steric and electronic variations of TMPyP4, including those which coordinated with various metal ions (*see* col. 44, lines 41-67; and Table 4 at col. 45). *Wheelhouse* found, among others, that "[t]hose complexes where the porphyrin offered an unhindered face for stacking were the better inhibitors, that is the square planar Cu(II) complex and pyramidal Zn(II)." However, *Wheelhouse* also discloses that "the larger ions do not fit in the center of the porphyrin but lie above the plane of the porphyrin ring so that even the formally square planar Au(III) complex was a poor inhibitor" (col. 44, lines 53-57; emphasis added). Indeed, Table 4 of *Wheelhouse* clearly demonstrated that the incorporation of Au(III) into the free-base porphyrin H_2TMPyP resulted in dramatically decrease in telomerase inhibitory activity (only 23% inhibition), compared to free-base TMPyP4 (88% inhibition) and TMPyP4 coordinated with other metals, such as Zn(II) (88% inhibition) and Co(II) (83% inhibition).

Thus, *Wheelhouse* actually teaches away from the present invention which uses the composition containing gold(III) porphyrins that exhibit potent cytotoxicity. Indeed, *Wheelhouse* repeatedly states that the effective telomerase inhibitors have low cytotoxicity against tumor cell lines (*see*, for example, col. 10, lines 56-60; col. 13, lines 17-21; and Example 3 at col. 38, in particular, col. 39, lines 4-10 and lines 21-24). Accordingly,

Wheelhouse would have strongly discouraged one skilled in the art to utilize metalloporphyrins containing gold(III) as telomerase inhibitors.

In literature, gold(III) ion has long been known to exhibit potent cytotoxicity, and the potential anti-cancer properties of different classes of gold(III) complexes have been extensively studied. However, none of the researchers had reported the cytotoxicity of gold(III) porphyrin complexes prior to the report by the present inventor. The rationale leading to the present invention was to use robust porphyrin ligand to stabilize cytotoxic gold(III) ion and, to that end, the inventor chose the porphyrin ligands primarily because of their intrinsic chelating properties, and also their roles in biological system (*e.g.*, iron-containing hemoglobin), as well as their being photodynamic therapeutic agents. The nature of the porphyrin ligand itself indeed is not a paramount issue regarding the anti-cancer properties of the resultant gold(III) porphyrin complexes, but the potent cytotoxicity of gold(III) is. This point was clearly demonstrated by showing the similar cytotoxic values (*i.e.*, IC_{50} = ~10^{-7} M) between the gold(III) porphyrins with neutral substituted groups and the unsubstituted gold(III) tetraphenylporphyrin (*e.g.*, "1a"; *see* Table 4a at page 40 of the present specification).

In contrast, coordination of gold(III) into the free porphyrin H_2TMPyP, the latter of which is specifically highlighted by *Wheelhouse*, exhibited significantly reduced overall anti-cancer property with IC_{50} values more than 10^{-4} M (col. 13, lines 17-21). This significant difference, by more than 1,000-fold, in cytotoxicity in the absence of the pyridinium/quinolinium structures and/or hydrogen bond accepting group (*i.e.*, unsubstituted gold(III) tetraphenylporphyrin) clearly indicates that the gold(III) porphyrin system of the present invention is quite a separate category of anti-cancer agents from those disclosed by *Wheelhouse*.

Furthermore, the Office Action consistently refers to the porphyrin structure shown at col. 4, lines 35-50, of *Wheelhouse* and the whole list of metal ions, including Au, for the "M" position (col. 4, lines 51-55), as well as a numerous, possible substituents for

Ar_1, Ar_2, Ar_3 and Ar_4, independently, listed at col. 4, line 56 through col. 9, line 12, particularly pointing to the substituent at col. 5, line 10-15, of *Wheelhouse*. However, nothing in *Wheelhouse* suggests to one of ordinary skill in the art that the gold(III) porphyrins as recited in the present claims, out of hundreds of millions of compounds covered by *Wheelhouse*, are the most promising anti-cancer agents due to their potent cytotoxicity (*In Takeda Chemical Industries, Ltd. v. Mylan Labs*, 417 F.Supp.2d 341, at 375 (S.D.N.Y. 2006), *aff'd*, (Fed. Cir. 2007) (No. 06-1329), "[t]he court, however, found nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties").

Furthermore, the Examiner has picked and chosen a specific metal and substituents out of numerous options disclosed by *Wheelhouse* to come up with the specific composition recited in the present application. Such is an impermissible hindsight reconstruction of the claimed invention. *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991) ("As in all determinations under 35 U.S.C. section 103, the decision-maker must bring judgment to bear. It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.").

In view of the above, Applicants believe *Wheelhouse* does not render present claims 1-4 and 58-59 obvious at all and the rejection of the claims under 35 U.S.C. § 103(a) as being obvious over *Wheelhouse* should be withdrawn.

Separately, however, claim 1 is herein amended to better reflect the anti-cancer activity of gold(III) porphyrins based on their potent cytotoxicity. Thus, claim 1 now reads, in the relevant portion, "[a] method for induction of cytotoxic effects . . . ."

Further, claim 1 is also amended to indicate that the cancer cells to be treated are hepatocellular carcinoma cells or nasopharyngeal carcinoma cells, as these two types of cancer are prevalent among the populations originated from South-East Asia. The amendment is solely to accelerate the prosecution of the case and Applicant expressly reserves a right to pursue in a continuation application the claims directed to the other types of cancer disclosed in the present application. Support for the amendment can be found, for example, at page 28, paragraph [00122], and Example 3 and Table 4a at page 40, of the specification. Hence, no new matter has been introduced by the amendments.

In addition, claim 13 is herein amended to correct a typographical error reciting "m is +3" to "m is -3". The error is obvious to one skilled in the art, but support for the amendment can be found in the compound, "(1k)", at page 24 of the specification.

In view of the foregoing amendments and remarks, applicant believes the pending application is now in condition for allowance, an early notification of which is earnestly requested.

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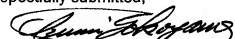
Respectfully submitted,

By 
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